Capecitabine-Based Combination Therapy for Breast Cancer: Implications for Nurses

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Purpose/Objectives: To review available data and implications for nurses of combination regimens containing capecitabine for metastatic breast cancer.

Data Sources: Peer-reviewed publications or abstracts from major oncology conferences and reviews of capecitabine focusing on nursing implications.

Data Synthesis: Capecitabine has proven efficacy in combination with docetaxel and is under evaluation in the neoadjuvant, adjuvant, and metastatic settings in combination with several oral and IV chemotherapeutic and biologic agents.

Conclusions: Capecitabine-containing regimens demonstrate high activity in a range of settings but typically have more complex safety profiles, dose-modification schemes, and scheduling requirements than monotherapy.

Implications for Nursing: Patients need to be aware of a wider range of likely side effects and should understand that they have been prescribed combination therapy rather than more simple, single-agent treatments because of its potential to improve outcome.

Most women diagnosed with breast cancer want up-to-date, high-quality information to help them better understand their likelihood of survival, available treatment options, and risk of recurrence (Gopal, Beaver, Barnett, & Ismail, 2005; Luker et al., 1995). Patients also need information about treatment side effects, self-care, and effects of the disease experience on family and social life (Luker et al.). Nurses should understand likely side effects fully to advise patients effectively and provide accurate and appropriate information, particularly concerning newly available treatment options (McGinn & Moore, 2001). Therefore, nurses should be aware of chemotherapy agents' side effects when used alone and in combination regimens. Nurses also should understand how administration routes may cause particular side effects. Oral administration avoids the complications and patient anxieties associated with IV administration (Cole, 2006; Cox & Fallowfield, 2007). In addition, many patients feel a sense of empowerment with oral chemotherapy because they are in control of their treatment; most patients with cancer prefer oral to IV therapy (Borner et al., 2002; Liu, Franssen, Fitch, & Warner, 1997; Paley et al., 2005).

Capecitabine (Xeloda®, Roche Laboratories, Inc.) is an oral drug designed to deliver cytotoxic 5-fluorouracil (5-FU) directly to the tumor site. Although capecitabine itself is inactive, the drug undergoes a three-stage conversion to cytotoxic 5-FU. The final stage requires the enzyme thymidine phosphorylase, which is present at significantly higher concentrations in tumor tissue than in normal tissue (Ishikawa et al., 1998; Miwa et al., 1998). The localization of thymidine phosphorylase means that 5-FU is generated preferentially in tumors; therefore, the risk of side effects resulting from cytotoxic activity in the gastrointestinal tract is reduced, increasing patient benefit.

The U.S. Food and Drug Administration (FDA) approved capecitabine in 1998 for the treatment of metastatic breast cancer resistant to paclitaxel and anthracycline-containing chemotherapy regimens or resistant to paclitaxel in patients for whom additional anthracycline therapy may be contraindicated. In 2001, capecitabine in combination with docetaxel (Taxotere®, sanofi-aventis U.S. LLC) was approved for patients with metastatic breast cancer that had progressed after treatment with an anthracycline-containing cancer therapy. The combination resulted in a significantly superior response rate, time to disease progression, and overall survival versus docetaxel alone in a randomized phase III trial (O'Shaughnessy et al., 2002).

Capecitabine has a unique safety profile. Alopecia and myelosuppression, common side effects of many chemotherapies used in breast cancer treatment, present infrequently with capecitabine. However, capecitabine is associated with some rare side effects, particularly palmar-plantar erythrodysesthesia, most often referred to as hand-foot syndrome by nurses (Mrozek-Orlowski, Frye, & Sanborn, 1999; Timmerman, 2001; Webster-Gandy, How, & Harrold, 2007; Wilkes & Doyle, 2005). Although the side effects present specific management challenge

for oncology nurses (Berg, 2006), capecitabine is advantageous for the development of combination regimens because of its high single-agent activity and unique safety profile that does not overlap with other chemotherapy agents (see Table 1). However, combination regimens generally are more complex than single-agent therapy and require greater understanding among nurses, who must prepare patients for treatment side effects and increased requirements for monitoring or tests. As a result, clinical data presented as peer-reviewed primary publications or abstracts at major oncology conferences were reviewed to identify emerging capecitabine-containing combination regimens for the treatment of women with breast cancer and to assess nursing implications for the new approaches.

Capecitabine: The Backbone of Combination Regimens?

Combination Regimens Versus Sequential Single Agents

Whether treatment is more effective when two drugs are given together as combination therapy or one drug is administered as a single agent and switched to another when the first ceases to be effective often is questioned. Sequential administration of single agents generally is accepted as the appropriate therapy for patients with less aggressive disease, for whom minimal toxicity and maintenance of quality of life are among the most important considerations, or for less fit patients who are unlikely to tolerate aggressive chemotherapy. Sequential administration lessens the risk of severe toxicity without compromising efficacy, so capecitabine monotherapy frequently is used in those patient populations. However, combination therapy is recommended in younger, fitter patients with rapidly progressing disease, lung or liver metastases, and other factors associated with a poor outcome. Combining two or more agents with high single-agent activity can increase efficacy, as demonstrated by the addition of capecitabine to docetaxel (Beslija et al., 2006; O'Shaughnessy et al., 2002). Combinations of agents that act together synergistically enable outcomes to be improved further and, therefore, are particularly desirable.

Challenges in Developing Individualized Combination Regimens

Individualization of treatment is an important goal in the care of women with breast cancer. Combination regimens often were developed by trial and error in the past, but now a more methodical approach usually is adopted with the vast array of agents available, facilitated by dramatic advances in the understanding of breast cancer biology, genetic profiling, and prognostic and predictive factors, such as HER2. Combinations of two or more agents are selected on the basis of high single-agent activity, nonoverlapping toxicities, and preclinical interactions.

Challenges in developing combination regimens include drug interactions, differing routes of administration (oral or IV), and identification of the optimal dose and schedule for each agent. The doses used when agents are administered in combination regimens typically are lower than when agents are used alone or sequentially. The FDA-approved docetaxel dosing schedule is capecitabine 1,250 mg/m^2 BID for 14 days in combination with docetaxel 75 mg/m^2 on day 1 every 21 days. However, a large proportion (65%) of the 251 patients treated with the combination in a pivotal randomized phase III trial required dose reduction of one or both agents because of adverse events (O'Shaughnessy et al., 2002). Detailed data analysis from the trial suggested that appropriate dose modification for toxicities did not impair efficacy (Leonard et al., 2006); lower capecitabine doses are used frequently in clinical practice, resulting in improved tolerability.

Table 1. Comparison of Grade III or IV Chemotherapy-Related Side Effects (in > 5%) for Monotherapy Agents

Side Effect	Capecitabine	Docetaxel	Paclitaxel[a]	Vinorelbine
Hand-foot syndrome	x			
Diarrhea	x	x		
Stomatitis	x	x		
Nausea and vomiting		x		
Myalgia and arthralgia		x	x	
Neurosensory		x	x	x
Asthenia and fatigue	x	x	x	x
Neutropenia		x	x	x
Thrombocytopenia		x		
Anemia		x		x
Febrile neutropenia		x		
Infections		x		
Fluid retention		x		
Cutaneous		x		
Alopecia		x		
Lymphopenia	x			
Dehydration	x			
Hypotension			x	
Leukopenia		x	x	x
Bilirubin	x			x

[a] Standard paclitaxel or nanoparticle albumin–bound paclitaxel

Note. Based on information from Abraxis Oncology, 2005; Bristol-Myers Squibb Company, 2007; Pierre-Fabre Pharmaceuticals, Inc., 2005; Roche Laboratories, Inc., 2006; sanofi-aventis U.S. LLC, 2007.

As a result, recent and ongoing randomized phase III trials in the metastatic and adjuvant setting have been designed to evaluate lower capecitabine and docetaxel doses in combination. Capecitabine doses should be tailored to individual patients for the duration of treatment irrespective of the starting dose. Nurses have a frontline role in educating patients, monitoring for side effects, and ensuring that doses are modified promptly when necessary (Mrozek-Orlowski et al., 1999). Nurses also should reassure patients that dose modification does not stop the treatment from working effectively and emphasize that modification ensures that capecitabine treatment can be continued for as long as possible.

Differences in the tolerability of fluoropyrimidines (e.g., capecitabine and 5-FU) according to geographic region also should be considered when identifying the optimal dose for capecitabine-based combination regimens. An analysis of patients with colorectal cancer receiving capecitabine- or 5-FU–based therapy in either the adjuvant or metastatic setting in three large, randomized trials showed that fluoropyrimidine-related toxicities were more common in American patients than in European or Asian patients (Haller et al., 2008). The finding was true for capecitabine as well as 5-FU, suggesting that the toxicity rates are a class effect of fluoropyrimidines rather than being specific to capecitabine. Cultural differences in patient behavior, genetic polymorphisms, and differences in dietary folate intake all have been suggested to explain the finding.

Capecitabine-Based Combination Regimens Across the Breast Cancer Spectrum

The combination of capecitabine and docetaxel is well established as treatment for HER2-negative, anthracycline-pretreated metastatic disease. The combination currently is being evaluated as first-line therapy for patients with metastatic disease and as treatment in patients with early-stage breast cancer as adjuvant therapy after surgery or as neoadjuvant therapy before surgery. Docetaxel is not the only agent that can be combined with capecitabine; many other cytotoxic agents lead to increased activity of thymidine phosphorylase, and combining these agents with capecitabine potentially increases the activity of capecitabine. Agents currently under intensive evaluation for combination with capecitabine include taxanes, vinca alkaloids, epothilones, anti–vascular epithelial growth factors, and anti-HER2/neu agents (see Table 2).

Metastatic Breast Cancer

Clinical outcomes and safety results from phase II and III studies of capecitabine-based combination regimens for women with metastatic breast cancer confirmed that the combination regimens generally appear to be more effective than single-agent regimens in selected patients, but increase the side-effect burden (see Table 3). Published studies support the increasing role of capecitabine in the treatment of women whose tumors overexpress HER2 (Bartsch et al., 2007; Schaller et al., 2007; Yamamoto et al., 2008). Capecitabine plus trastuzumab was shown to significantly improve time to progression (the primary endpoint) compared with capecitabine alone in patients with HER2-positive metastatic disease progressing with previous trastuzumab-containing therapy (von Minckwitz et al., 2008). In addition to the high activity seen with capecitabine plus docetaxel doublet combinations, one randomized trial demonstrated that adding capecitabine to first-line trastuzumab plus docetaxel significantly improved time to disease progression and progression-free survival (Wardley et al., 2006). The success of combination therapy depends on the careful selection of individuals likely to benefit from a more intensive treatment strategy and the provision of effective support for patients to ensure compliance with therapy and minimize treatment-related complications.

Table 2. Agents Under Evaluation for Capecitabine Combination Therapy

Class	Agent
Anti-HER2	Lapatinib, trastuzumab
Anti–vascular endothelial growth factor	Bevacizumab, sunitinib
Epothilone	Ixabepilone
Taxane	Nanoparticle albumin–bound paclitaxel, paclitaxel, docetaxel
Vinca alkaloid	Vinorelbine (oral and IV)

Early-Stage Breast Cancer

Several large studies of capecitabine-based combinations as preoperative therapy for women with early-stage breast cancer have been reported (Berton-Rigaud et al., 2008; Lee et al., 2008; Wildiers et al., 2008; Zambetti et al., 2008) with additional trials currently being conducted. The high degree of activity (pathologic complete response = 15%–21%) demonstrated with capecitabine-based combination regimens administered before surgery suggests that the regimens also will be effective as adjuvant (postoperative) therapy. Interim safety results from the FinXX trial in the adjuvant setting indicated that the integration of capecitabine into an anthracycline- and taxane-containing sequential schedule was feasible (Joensuu et al., 2007).

Table 3. Outcomes and Toxicities of Capecitabine-Containing Combination Regimens in Breast Cancer

Disease Type and Combination	Clinical Outcome	Most Common (> 5%) Grade III or IV Toxicities	Reference(s)
HER2-Positive Disease			
Trastuzumab	Capecitabine plus trastuzumab significantly improves response rate, time to progression, and progression-free survival versus capecitabine alone in patients with HER2-positive metastatic disease progressing on trastuzumab-containing therapy; high activity seen in trastuzumab-naive patients.	HFS, pain, impaired motor function, nausea, diarrhea, hyperbilirubinemia, anemia, leukopenia, neutropenia, cardiac effects	Bartsch et al., 2007; Schaller et al., 2007; von Minckwitz et al., 2008; Yamamoto et al., 2007
Trastuzumab plus docetaxel	Significantly improved time to progression and progression-free survival; one- and two-year overall survival rates favor the capecitabine-containing arm.	HFS, febrile neutropenia, diarrhea, alopecia	Wardley et al., 2008
Trastuzumab plus oral vinorelbine	High response rate and encouraging progression-free survival in a single-arm study	Neutropenia, leukopenia, HFS, diarrhea, vomiting, fatigue, febrile neutropenia	Chan et al., 2008
Lapatinib	Lapatinib plus capecitabine is superior to capecitabine alone in patients with HER2-positive disease after treatment with anthracyclines, taxanes, and trastuzumab.	Diarrhea, HFS	Geyer et al., 2006
HER2-Negative Disease			
Docetaxel	Combination improves outcome compared to docetaxel alone; similar efficacy to epirubicin-docetaxel and gemcitabine-docetaxel	HFS, stomatitis, diarrhea, fatigue, neutropenia, febrile neutropenia, mucositis, alopecia, asthenia, nausea	Beslija et al., 2006; Chan et al., 2008; Mavroudis et al., 2008; O'Shaughnessy et al., 2002; Soto et al., 2006
Docetaxel plus bevacizumab	Promising response rate observed.	Neutropenia, HFS, fatigue, febrile neutropenia, diarrhea, nausea, stomatitis	Perez et al., 2006
Bevacizumab	Adding bevacizumab increased response rate, although progression-free survival was not improved in heavily pretreated patients.	HFS, diarrhea, hypertension, thrombotic events, asthenia	Miller et al., 2005; Sledge et al., 2007
Paclitaxel	Combination appears to be as effective as an anthracycline plus taxane.	Neutropenia, leukopenia, alopecia, HFS, fatigue, diarrhea, pain	Blum et al., 2006, 2007; Gradishar et al., 2004; Lueck et al., 2006; Soto et al., 2006
Nab-paclitaxel	Single-arm study showed activity.	HFS, fatigue, neutropenia, mucositis	Somer et al., 2007
Oral vinorelbine	No less effective than IV vinorelbine	Vomiting, neutropenia, leukopenia, febrile neutropenia, stomatitis, fatigue, infection with neutropenia	Lorusso et al., 2006; Tubiana-Mathieu et al., 2008
IV vinorelbine	Combination of vinorelbine and capecitabine shows activity in a range of settings	Neutropenia, febrile neutropenia, asthenia	Ghosn et al., 2006, 2008
Ixabepilone	Addition of ixabepilone provides modest clinical improvement in progression-free survival but not overall survival.	Leukopenia, anemia, thrombocytopenia, neutropenia, peripheral neuropathy, myalgia, fatigue, HFS, diarrhea	Hortobagyi et al., 2008; Thomas et al., 2007

HFS—hand-foot syndrome; Nab—nanoparticle albumin-bound

Capecitabine-Based Combinations Versus Monotherapy

Efficacy: A critical difference between capecitabine monotherapy and capecitabine-based combination regimens is the potential for improved outcomes in patients eligible for more aggressive treatment. Although capecitabine monotherapy is highly active and appropriate for certain patients, including those with less aggressive disease or those who do not require a rapid response (Soto et al., 2006), combination therapy, if tolerable, often is the preferred approach in patients who have a high tumor burden, are young and fit, or have imminent risk of organ failure. In

addition, combining capecitabine with single agents improves efficacy, as demonstrated by the phase III trial evaluating capecitabine plus docetaxel (O'Shaughnessy et al., 2002). Nurses already are familiar with the benefits of adding capecitabine to docetaxel; similar benefits appear likely with paclitaxel, trastuzumab, and possibly other agents, including bevacizumab.

Side-effect profile: Administering combination treatment increases the complexity of side-effect profiles, which nurses should understand to prepare patients for treatment side effects (see Table 4). Patients also may require additional monitoring or tests; for example, a patient receiving capecitabine in combination with vinorelbine will require regular hematologic monitoring for the development of severe neutropenia, which occurs with vinorelbine, as well as monitoring for early symptoms of hand-foot syndrome and gastrointestinal effects, which are characteristic of capecitabine. In addition, administering two or more agents in combination usually makes dose-modification schemes more complex. By assessing which agent likely is causing a particular side effect, nurses will be able to determine whether one or both drugs will require dose reduction.

Implications for Nursing

Nurses have a pivotal role in helping patients avoid, cope with, or overcome side effects of cancer treatment (Boehmke & Dickerson, 2005). Oral administration, rather than decreasing patient care effort, requires nurses to spend more time with patients, educating them about their treatment and helping them to recognize and manage side effects. Nurses can use a vast array of techniques and educational aids (e.g., frequent telephone follow-up, patient diaries, pocket guides) to teach patients how to take treatment correctly as well as recognize and manage side effects (Berg, 2006; Gerbrecht, 2003; Moore, 2007; Mrozek-Orlowski et al., 1999; Viale, Fung, & Zitella, 2005). Oral administration also enables nurses to spend more time caring for patients by freeing them from the practical requirements of IV administration.

Management of Specific Adverse Events

Hand-foot syndrome is a frequent side effect of capecitabine and should be managed proactively so patients can continue with treatment (Lassere & Hoff, 2004; Marse, Van Cutsem, Grothey, & Valverde, 2004; Webster-Gandy et al., 2007; Wilkes & Doyle, 2005). When grade II or III hand-foot syndrome occurs during the first two cycles of capecitabine, additional treatment should be delayed until symptoms resolve or decrease to grade I intensity (Wilkes & Doyle). Capecitabine dose reduction is recommended for patients developing

Table 4. Adverse Effects Comparison for Capecitabine Monotherapy and Combination Therapy

	Patients Reporting Any Grade (%)	
Side Effects	Capecitabine With Anthracycline and Paclitaxel Pretreatment (N = 162)	Capecitabine Plus Docetaxel With Anthracycline Pretreatment (N = 251)
Diarrhea	57	67
Nausea	53	45
Vomiting	37	35
Stomatitis	24	67
Abdominal pain	20	30
Constipation	15	20
Dyspepsia	8	14
Dry mouth	–	6
Hand-foot syndrome	57	63
Alopecia	–	41
Dermatitis	37	8
Rash erythematous	–	9
Nail disorder	7	14
Nail discoloration	–	6
Fatigue	41	22
Pyrexia	12	28
Pain in limb	6	13
Pain	–	7
Lethargy	–	7
Asthenia	–	26
Weakness	–	16
Paresthesia	21	12
Peripheral neuropathy	–	6
Taste disturbance	–	16
Headache	9	15
Dizziness	8	12
Insomnia	8	8
Anorexia	23	13
Appetite decreased	–	10
Weight decreased	–	7
Dehydration	7	10
Lacrimation increased	–	12
Eye irritation	15	5
Arthralgia	–	15
Myalgia	9	15
Back pain	–	12
Bone pain	–	8
Edema	9	33
Neutropenic fever	–	16
Dyspnea	–	14
Cough	–	13
Sore throat	–	12
Epistaxis	–	7
Oral candidiasis	–	7
Urinary tract infection	–	6
Leukopenia	–	91
Neutropenia	26	86
Thrombocytopenia	24	41
Anemia	72	80
Lymphopenia	94	99
Hyperbilirubinemia	22	20

Note. Based on information from Roche Laboratories Inc., 2006.

grade III hand-foot syndrome. In addition to dose modification, symptomatic relief can be provided with hand creams and topical emollients (Chin et al., 2001; Wilkes & Doyle). Nurses also should instruct patients about specific measures that can minimize hand-foot syndrome (e.g., taking cold or cool baths, applying cold compresses or ice packs to the hands and feet, preventing mechanical pressure on deep capillaries) (Moore, 2007; Wilkes & Doyle). Although the measures were developed for patients receiving capecitabine as monotherapy, they also are valuable to minimize hand-foot syndrome associated with combination regimens.

Patients require heightened monitoring for bone marrow suppression and its clinical consequences when capecitabine is combined with anthracyclines, taxanes, vinorelbine, or ixabepilone. Hematologic toxicity usually is manageable with dose modification, but hematopoietic growth factors may be required occasionally. Prophylactic antibiotics may be indicated in patients experiencing neutropenia and diarrhea (Marse et al., 2004). Gastrointestinal symptoms (e.g., vomiting, diarrhea) may require dose reductions and intensive fluid management (Moore, 2007). Some patients may require antiemetics, and nurses should provide guidance and appropriate symptom management (Dibble, Casey, Nussey, Israel, & Luce, 2004). Mucositis and stomatitis can be treated with antiseptic mouthwashes and pain relief (Cawley & Benson, 2005). Analgesics also may provide effective relief of myalgias and arthralgias commonly seen in patients receiving taxanes (Markman, 2003). Alopecia is a distressing side effect of taxanes, and nurses should prepare patients for profound hair loss by recommending that they get a short haircut before the first treatment and wear a wig (Markman). Although a variety of side effects may occur when capecitabine is administered as monotherapy, nurses should familiarize themselves with a far broader range of adverse effects and learn how to successfully manage them in patients receiving capecitabine-containing combination regimens.

Patient Education and Information

Self-care can help patients manage and even overcome the side effects of treatment with effective education (Williams & Schreier, 2004). Patients should recognize when to seek professional help so that side effects can be managed effectively and steps can be taken to prevent recurrence.

Capecitabine doses occasionally need to be tailored to an individual's tolerable level, but patients may fear that treatment will be less effective and, therefore, be reluctant to reduce the dose. As a result, nurses must maintain excellent patient education and communication skills to reassure patients that the efficacy of their treatment will not be reduced if the dose has to be modified to a level that the individual can tolerate. Widespread capecitabine monotherapy use enabled nurses to refine their education and communication skills because they spent less time administering IV treatment and more time focusing on adherence to oral treatment, often with frequent telephone calls or home visits. The broader use of home-based oral chemotherapy has decreased the time patients spend at the clinic, so nurses have become an important link between patients and the healthcare team. Written information (e.g., educational materials, pill diaries, toxicity recording sheets) is useful and requires nurses to support patients during treatment and spend time teaching them how to use the tools. Individual patient needs and learning preferences should be matched with available resources (Moore, 2007). The value of separate patient education visits has been emphasized (Hartigan, 2003), and the majority of patients prefer to receive information via written materials or discussions with healthcare professionals (Smith et al., 2004). A wide range of tools and guides have been used effectively by patients receiving treatment with capecitabine, including printed brochures and computer-assisted instruction, but not all patients have access to computers and the Internet (Chau, Legge, & Fumoleau, 2004; Faithfull & Deery, 2004; Gerbrecht & Kangas, 2004; Moore). In addition, nurses should provide patients receiving capecitabine in combination with other chemotherapy agents with additional materials about the drugs they are taking.

Noncompliance, a major threat to successful oral chemotherapy (Moore, 2007; Partridge, Avorn, Wang, & Winer, 2002), is associated with multiple factors, including misinterpretation of physician instructions, denial, forgetfulness, distraction or confusion, polypharmacy syndrome, cost of drugs, number of tablets, dosing frequency, and side effects (Moore). Nurses can improve compliance by increasing patient trust and comfort levels with the treatment program and its potential benefits through discussion and support. In addition, nurses should ensure that patients adhere to dose modifications made during the course of capecitabine therapy, particularly if patients receive capecitabine from a mail order pharmacy because the dosing information may not match the current dosing protocol (Moore). In a phase III trial of 23 patients with colorectal cancer, 96% (22) always remembered to take their capecitabine tablets (Rough, MacLeod, Cassidy, & McDonald, 2004). Overdosing also may be an issue with self-administered oral therapy but rarely is a concern when an oncologist prescribes IV chemotherapy. Patient education on individual dose adjustment is critical to avoid potentially life-threatening toxicities. Nursing management challenges are increased in patients receiving combination therapies or concomitant medications for chemotherapy-related side effects or the treatment of comorbidities; interactions may occur between capecitabine and warfarin, phenytoin, and antacids (Moore). Possible interactions among concomitant medications and other chemotherapy drugs also should

be considered in patients receiving capecitabine-based combination regimens.

Conclusions

As monotherapy, capecitabine represents an effective and well-tolerated oral therapy in a range of treatment settings for breast cancer. As the foundation of combination regimens with traditional chemotherapeutic agents or novel biologic agents, capecitabine may further improve outcomes for patients. Combination partners expected to be used more frequently in clinical practice with capecitabine are paclitaxel, trastuzumab, and bevacizumab. All oral combination regimens (e.g., capecitabine plus lapatinib in HER2-positive metastic disease) may lead to additional changes in the responsibilities of nurses caring for patients with breast cancer. The role of nurses in educating patients, explaining treatments, recognizing and managing side effects, and minimizing treatments' interference with patients' lives is pivotal to optimal care. Nurses' roles will continue to expand as highly active agents are combined to improve outcomes for patients with breast cancer.

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